PATENT

1-30-87

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	David B. Anderson, et al.	10
Serial No.:	860,719	
Filed :	May 7, 1986	Group Art Unit: 125
For :	GROWTH PROMOTION	
Docket No.:	X-5683C	

DECLARATION UNDER 37 C.F.R. 1.132

Commissioner of Patents and Trademarks

Washington, D.C. 20231

Sir:

I, David B. Anderson, hereby declare and say as follows:

I received a Bachelor of Science degree in 1966 from South Dakota University in the field of Animal Science. I received an M.S. degree in Animal Science in 1968 from the University of Wisconsin and a Ph.D. from the same institution in 1971 in Biochemistry and Animal Science.

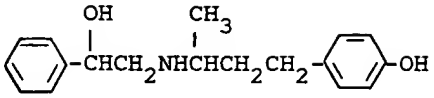
From 1972 to 1975 I was Chief of the Biochemistry Branch of the Aeromedical Research Laboratories of the U.S. Army. From 1975 to 1979, I was Assistant Professor of Animal Science at the University of Illinois. In 1979 I joined Eli Lilly and Company as a Senior Scientist in the Animal Nutrition Research Division. I was promoted to Research Scientist in 1983. Since 1979, I have been responsible for conducting and supervising basic and applied research for Eli Lilly and Company in the area of animal nutrition and animal growth.

I am one of the inventors named in the above-captioned patent application. I am familiar with the subject matter of that application and in particular the invention as claimed in

Claims 35, 36, 37, and 38. I have evaluated the compound recited in those claims for its ability to promote growth and improve feed efficiency in animals. I have evaluated the compound both as a mixture of all four optical isomers, and I have more recently evaluated two of the pure optical isomers that comprise the mixture. The evaluation of the individual isomers was carried out according to the following procedure.

Eight crossbred barrows, each weighing approximately 70 kg. and maintained in individual metabolism cages, were employed for the study. These animals were accustomed to a feeding regime of 1600 g. of feed per day divided into two equal feedings. These feeding regimes were maintained throughout the study and the animals received water ad libitum. The pigs were fasted for approximatley 40 hours before the test was initiated in order to establish a base line of serum free fatty acid levels. Two of the animals were used as control and received the normal feeding regime and the carrier used to administer the drug to the other animals. Two animals received the Mills et al. compound of its Example 11, which is a pure R,S isomer of a β-phenethanolamine.

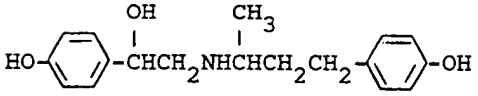
Another set of two animals received the pure R,S isomer of the compound required for the present invention, which is identified within Eli Lilly and Company as 99417. Both the Mills compound and 99417 were administered at a dose of 500 mcg. per kg. The R,R isomer of the compound required the practice of the now claimed invention, which is identified within Lilly as 99134, was administered to the remaining group of two animals at a dose of 50 mcg. per kg. The structure of the test compounds are shown below.



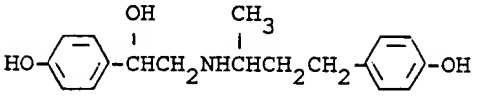
Mills et al.

Example 11

79771



99417



99134

Blood samples from all of the animals were taken from the indwelling femoral catheters 120 minutes and 15 minutes prior to feeding and prior to administration of the test compound on the day of the evaluation. The serum samples were assayed for free fatty acid content by an enzymatic procedure. After the animals had been fasted and the base line free fatty acid level had been established, the animals were fed their normal daily feed regime along with the indicated drug administrations. Serum samples were drawn on an hourly basis up to six hours following feeding and treatment, and the samples were analyzed for free fatty acid content. The results of this study are presented in the following table.

Treatment	Level, mcg/kg	N	Serum Free Fatty Acids (μmoles/ℓ) Pre	+1 Hr	+2 Hr	+3 Hr	+4 Hr	+5 Hr	+6 Hr
Control	--	2	561	81	58	84	68	68	56
79771	500	2	542	48	34	55	49	66	67
99417	500	2	566	130	70	90	65	64	48
99134	50	2	571	1220	524	285	236	160	178

The data establish that 79771, the Mills R,S compound, caused essentially no affect on free fatty acids relative to untreated control animals. The R,S isomer of the invention compound, 99417, caused a slight elevation in serum free fatty acids. Applicants' pure R,R isomer, 99134, effected a substantial increase in free fatty acid serum concentrations, even after six hours following drug administration, and at a dose one tenth of that at which the Mills 79771 compound and the 99417 compound were evaluated. As indicated by lipolytic response, the data establish that the pure R,R isomer of the invention compound is responsible for most of the growth promotion activity and feed efficiency improvement activity observed in swine by administering a mixture of the compounds or the pure R,R-isomer.

I further declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both (18 U.S.C. 1001), and may jeopardize the validity of the application or any patent issuing thereon.

David B. Anderson

12/24/86